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February 4, 2004

BY HAND DELIVERY

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, Maryland 20852

RE: Docket No. 03P-0519 – Comments in Opposition to Abbott Laboratories Citizen Petition for ANDA Suitability of Ondansetron Hydrochloride Injection and Ondansetron Hydrochloride Premixed.

Dear Sir or Madam:

The above-referenced petition should be denied because it proposes changes that are not authorized for approval through an ANDA suitability petition. Compared to the current product labeling, the proposed changes would introduce one higher-than-approved, and five lower-than-approved, single-unit doses of ondansetron hydrochloride. Although characterized by the petitioner as "new dosage forms," six of the seven proposed changes are new dosing regimens, which may not be authorized through an ANDA suitability petition.

Even if FDA were to deem the changes petitionable, it should deny the petition on one or more grounds. New dosing regimens, like the ones proposed, typically require clinical investigation and significant labeling changes, both of which are grounds for denial.

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Indeed, even if FDA accepts the petitioner's own characterization of the proposed changes, the petition must be denied because the safety and effectiveness of any "new dosage form" – including one proposed through an ANDA suitability petition – must be studied in the pediatric population. Moreover, marketing so many different single-dose units of the same drug introduces the risk of confusion. FDA is not required to authorize changes that would heighten the risks associated with the product.

Notwithstanding the arguments set forth herein, if FDA approves the ANDA suitability petition, in whole or in part, it should remind the petitioner that two of the proposed changes (i.e., the two prefilled syringe products) will be subject to the 180-day exclusivity, if any, of a first filer of a paragraph IV certification for the reference listed drug.

Background

On November 6, 2003, Abbott Laboratories ("Abbott" or "petitioner") filed the above-referenced citizen petition requesting that the Food and Drug Administration ("FDA") permit that abbreviated new drug applications ("ANDAs") be filed for ondansetron hydrochloride injection (4 mg/2 ml and 8 mg/4 ml) in prefilled single-dose syringes and ondansetron hydrochloride injection premixed (8, 12, 16, 20, and 24 mg in 50 ml 5% dextrose injection) in single-dose, flexible plastic containers (hereinafter the "citizen petition"). The listed drug, Zofran (ondansetron hydrochloride) Injection and Injection Premixed, is manufactured by GlaxoSmithKline ("GSK") and is available as follows: 2 mg/ml in a 2 ml single-dose vial; 2 mg/ml in a 20 ml multi-dose vial; and premixed 32 mg/50 ml in 5% dextrose in a single-dose flexible plastic container. According to Zofran labeling, the appropriate dose for prevention of post-operative nausea and vomiting is 4 mg, undiluted, which can be given as a single injection, and the appropriate dose for prevention of chemotherapy-induced nausea and vomiting is 32 mg, diluted in 50 ml of 5% dextrose or normal saline, administered over 15 minutes.

As set forth herein, FDA should deny Abbott's request. Six of the seven proposed products provide ondansetron in single-unit doses that differ from the dosing regimen set forth in the approved product labeling. That is, while Abbott characterizes its proposed

changes as "additional dosage forms," six out of seven are in fact single-dose units, each of which contain an amount of ondansetron that differs from what is described in the approved product labeling as the appropriate dose.

Because of the manner in which the approved labeling directs the product be administered – a single undiluted 4 mg dose to prevent post-operative nausea and vomiting or a single 32 mg diluted dose to prevent chemotherapy-induced nausea and vomiting – Abbott's proposed new single-unit "dosage forms" are changes in the dosing regimen described in the approved product labeling. The changes proposed by Abbott introduce one higher-than-approved single dose (8 mg undiluted) and five lower-than-approved single doses (8, 12, 16, 20, and 24 mg diluted). Marketing so many different single-dose packages of the same drug product also introduces the risk of confusion, which may lead to patients being administered the wrong dose.

FDA should deny Abbott's request because changes from the approved dosing regimen are not the type of change appropriate for an ANDA suitability petition. Moreover, such changes typically require clinical studies and significant changes to product labeling, both of which are grounds for FDA denial of an ANDA suitability petition. Even if FDA accepts Abbott's own characterization of the changes it proposes (i.e., new "dosage forms"), the petition still must be denied. The safety and effectiveness of any new dosage form proposed in an application submitted under the Food, Drug, and Cosmetic Act ("FDCA") section 505, 21 U.S.C. § 355, must be studied in the pediatric population.

In the event that FDA grants Abbott's request with respect to the two prefilled syringe products, it should remind Abbott that those products are not different from, and are therefore subject to, the 180-day exclusivity, if any, of a generic version of the 2 mg/ml vial products.

Regulatory Framework

Section 505 of the FDCA authorizes the submission of ANDAs, which must include, among other things, information to show that the proposed new drug product has the same route of administration, dosage form, and strength as the already approved listed drug to which the application refers. 21 U.S.C. § 355(j)(2)(A)(iii). An ANDA for a drug product

with a different route of administration, dosage form, or strength may be approved only if the change from the listed drug is first authorized through approval of a suitability petition. Id. § 355(j)(2)(C).

FDA regulations authorize the submission of an ANDA for a drug "which is not identical to a listed drug in route of administration, dosage form, and strength," upon the approval of a suitability petition. 21 C.F.R. § 314.93(b).[1] The regulations specify the type of changes (route of administration, dosage form, and strength) from the listed drug that are appropriate for a suitability petition. No other type of change may be authorized by a suitability petition. See id. § 314.93(a).

Moreover, FDA must deny any ANDA suitability petition where investigations are required to demonstrate the safety and effectiveness of the proposed change to the drug or where the proposed change requires significant labeling changes to ensure safe and effective use. 21 C.F.R. § 314.93(e)(1)(i), (iv). While a change of drug strength is appropriate for review though a suitability petition, a change in dose or dosing regimen is not because 1) it is not the type of change authorized under Section 505(j)(2)(c) and 2) it would typically require clinical studies and significant labeling changes.

Summary of Abbott's Proposed Changes

Table 1 summarizes the changes proposed in Abbott's suitability petition. With the exception of the first proposed change – 4 mg ondansetron in a single-dose prefilled syringe, instead of a single-dose vial – each of the proposed changes would result in providing the drug in a new unapproved single-dose unit.

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[1] The substitution of one active ingredient in a combination drug product may also be authorized through a suitability petition. 21 C.F.R. § 314.93(b). That type of change, however, is not at issue here.

Table 1

Products Marketed by GSK	**Proposed by Abbott**	**Approved Dosage & Administration[2]**
4 mg/2 ml single-dose vial (2 mg/ml in a 2 ml vial)	4 mg/2 ml prefilled syringe (2 mg/ml in a 2 ml syringe)	**Prevention of post-operative nausea and vomiting** **Adults:** 4 mg undiluted IV immediately prior to anesthesia, or post-operatively if nausea and vomiting occurs (can be given in a single injection.) **Pediatric Population** Single 0.1 mg/kg dose for patients weighing 40 kg or <; or a single 4 mg dose for patients weighing > 40 kg.
	8 mg/4 ml prefilled syringe (2 mg/ml in a 4 ml syringe)	
40 mg/20 ml multiple dose vial (2 mg/ml in a 20 ml vial)		
Premixed 32 mg/50 ml	Premixed 8 mg/50 ml 12 mg/50 ml 16 mg/50 ml 20 mg/50 ml 24 mg/50 ml	**Prevention of nausea and vomiting (chemotherapy induced)** **Adults** 32 mg over 15 minutes, 30 minutes prior to chemotherapy or split into 3 doses of 0.15 mg/kg. The first dose is administered as above and the subsequent doses at 4 and 8 hours thereafter. **Pediatric Population** 4 to 18 years of age: three doses at 0.15 mg/kg. [If the vial is used, it must be diluted in 50 ml of 5% dextrose or normal saline.]

[2] Zofran (ondansetron) package insert.

Discussion

I. Abbott's request should be denied because the products it proposes introduce new doses or dosing regimens, which require clinical studies and significant changes to product labeling.

Abbott's request should be denied with respect to the following six out of seven proposed changes, each of which would introduce a new dosing regimen not described in approved product labeling:

- 8 mg/4 ml prefilled syringe;
- 8 mg/50 ml premixed;
- 12 mg/50 ml premixed;
- 16 mg/50 ml premixed;
- 20 mg/50 ml premixed; and
- 24 mg/50 ml premixed.

Abbott characterizes its proposed changes as "additional dosage forms," but because each of the new "dosage forms" listed above is a single-dose unit that contains an amount of ondansetron that differs from what is described in the approved product labeling, Abbott is actually proposing new doses or dosing regimens. Even if FDA accepts Abbott's characterization of the changes as "new dosage forms," the petition should still be denied because applications – including suitability petitions – submitted under FDCA section 505 that propose, among other things, "a new dosage form" require studies to assess safety and effectiveness in the pediatric population.

The innovator, GSK, provides Zofran (ondansetron) as follows:

1) 4 mg/2 ml single-dose vial (4 mg, undiluted, as a single injection, is the approved adult dose for the prevention of post-operative nausea and vomiting);

2) 40 mg/20 ml multi-dose vial; and

3) 32 mg/50 ml in 5% dextrose, premixed in a single-dose flexible plastic container (32 mg diluted in 50 ml of 5% dextrose, given over 15 minutes, is the approved adult dose for prevention of chemotherapy-induced nausea and vomiting).

The changes proposed by Abbott would introduce one higher-than-approved single dose of undiluted ondansetron (i.e., 8 mg/4 ml in a single-dose prefilled syringe) and five lower-than-approved single doses of diluted ondansetron (i.e., 8, 12, 16, 20, and 24 mg/50 ml single-dose flexible plastic containers).

There are at least two separate and distinct reasons that Abbott's request should be denied. First, a change to the dose or dosing regimen is not the type of change authorized for approval through an ANDA suitability petition. Second, even if we were to assume for the sake of argument that such a change is petitionable, introducing these new doses of the approved product raises questions of safety and effectiveness that require FDA to deny the petition. See 21 C.F.R. § 314.93(e)(1)(i), (iv).

Abbott has proposed changes that are not authorized for approval through an ANDA suitability petition.

Changes in dose or dosing regimen are not the type of change that can be authorized through an ANDA suitability petition. An ANDA for a drug product with a different route of administration, dosage form, or strength may be approved if the change from the listed drug is first authorized through approval of a suitability petition. 21 U.S.C. § 355(j)(2)(C). FDA regulations authorize the submission of an ANDA for a drug "which is not identical to a listed drug in route of administration, dosage form, and strength," upon the approval of a suitability petition. 21 C.F.R. § 314.93(b). Only these specific types of changes, i.e., route of administration, dosage form, and strength, are appropriate for a suitability petition. No other type of change may be authorized by a suitability petition. See id. § 314.93(a).

Since each of Abbott's proposed changes result in new single-unit doses, the petition must be denied as one not authorized under Section 505(j)(2)(C) of the FDCA. FDA routinely denies such ANDA suitability petitions. See, e.g., Letter from Buehler to Pharmaceutical Associates, Inc. of 7/9/02 (denying a request to change the strength and volume of drug product administered per dose of hydrocodone bitartrate and acetaminophen oral solution, where the change of volume of product per dose changed the dosing regimen, and noting that the change in dosing regimen was "not petitionable").

The petitioner characterizes the changes it proposes as changes in "dosage form" when they are actually changes in dose. Indeed, the text of the petition itself is inconsistent on this point. The petitioner demonstrates that it is proposing a new dose for prevention of post-operative nausea and vomiting when it attempts to set forth a medical rationale for the

proposed changes: "A review of trials by Tramer et al, indicated that an 8 mg dose may also be used intravenously for post operative nausea and vomiting." Citizen Petition at 3 (emphasis added). If the petitioner were not proposing a new dose, there would be no reason to focus on, or so characterize, this observation by Tramer.

Moreover, Abbott has taken this observation out of context. Tramer, which is a literature review (i.e., analysis of published studies), states the following in its discussion section:

> The lowest intravenous dose tested, 1 mg, was not significantly different from placebo . . . Increasing the dose beyond 8 mg, on the other hand, did not further improve long-term efficacy (at 48 h). The optimal intravenous dose of ondansetron to prevent [post-operative nausea and vomiting "PONV"] is likely to be 8 mg for long-term efficacy, although intravenous doses between 4 mg and 8 mg were not tested in these trials.

Citizen Petition, Exhibit III.

Tramer also recognized that the manufacturer (and FDA) had already determined the appropriate dose and described it in the labeling: "[T]he manufacturer has run an extensive clinical research program to establish the optimal dose and route of administration. The manufacturer concluded that in adults, 4 mg ondansetron was the best intravenous dose for preventing PONV." Citizen Petition, Exhibit III.

Even if FDA deems Abbott's proposed changes petitionable, the requests should be denied because the new doses raise questions of safety and effectiveness that would require clinical study and significant labeling changes.

FDA must deny an ANDA suitability petition where investigations are required to demonstrate the safety and effectiveness of the proposed change to the drug or where the proposed change requires significant labeling changes to ensure safe and effective use. 21 C.F.R. § 314.93(e)(1)(i), (iv). While a change of a drug product's strength is appropriate for review though a suitability petition, a change in dose or dosing regimen, like the ones Abbott proposes, are not because they would require clinical studies and significant labeling changes.

The petitioner's own description of, and cited support for, its "medical rationale" for the proposed changes demonstrates the importance of clinical studies and appropriate

labeling of the newly-proposed dosing regimens. Yet, the published studies on which the petitioner relies appear to lack the rigor demanded by FDA to demonstrate the safety and effectiveness of a drug product.

For example, the petitioner indicates that a study by Bernstein and Ong "determined that 8 mg ondansetron IV combined with dexamethasone was effective in controlling nausea and vomiting in patients receiving moderately and highly emetogenic chemotherapy." Citizen Petition at 3. The study reported by Bernstein and Ong studied only 38 patients, was an open-label design, and lacked any control group. Citizen Petition, Exhibit IV. Even if FDA were to deem this study adequate, Abbott does nothing to address the concomitant use of dexamethasone in its proposed product labeling. Similarly, the other published reports relied on by the petitioner include two open-label studies conducted in Italy more than eight years ago. Citizen Petition, Exhibits V and VI.

The petitioner also highlights the importance of describing the new doses in product labeling by characterizing the proposed new doses in premixed containers as follows:

> Ready to use premixed containers also reduce the risk of compounding error by providing a dosage form that comes labeled from the manufacturer. The clinician inserts an administration set and the drug is ready for infusion.

Citizen Petition at 3 (emphasis added).

Moreover, marketing many different single-dose packages of the same drug product, as Abbott proposes, introduces the risk of confusion, which may lead to patients being administered the wrong – and potentially ineffective – dose. FDA is not required to approve a change under FDCA section 505(j)(2)(C) that would heighten the risks associated with the product. See, e.g., Letter from Buehler to Lipomed, Inc of 8/1/01 (denying ANDA suitability petition where the applicant proposed "doubling of the dose" of cladribine and noting that the agency is not required to approve changes under section 505(j)(2)(C) that involve a heightened risk associated with use of the product).

Even where FDA has deemed a proposed change to be one that is appropriately authorized under Section 505(j)(2)(C) of the FDCA (e.g., a change to either a higher or a lower strength), it has routinely denied ANDA suitability petitions that – like the one at issue here – raise questions of safety and effectiveness that would require clinical studies

and significant labeling changes to ensure safe use. See, e.g., Letter from Buehler to Shotwell & Carr, Inc. of 7/3/02 (denying petitioner's request to change strength from 350 mg to 200 mg carisoprodol tablets because FDA had no information to indicate the lower dose would be effective for the labeled indications) and Letter from Buehler to TestoCreme, LLC of 4/12/02 (denying petitioner's request to change strength from 1% testosterone topical gel to 5% testosterone topical gel).

If FDA accepts petitioner's own characterization of the changes it proposes, the petition still must be denied because new dosage forms require pediatric study.

As noted above, the petitioner characterizes the changes it proposes as changes in "dosage form." Citizen Petition at 2. Applications submitted under section 505 of the FDCA "for a new active ingredient, new indication, new dosage form, or new route of administration" require pediatric studies. Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, codified at 21 U.S.C. § 355B(a)(4)(A) (emphasis added).

On October 17, 2002, the U.S. District Court for the District of Columbia invalidated FDA's pediatric rule[3] and enjoined the agency from enforcing it. Ass'n of Am. Physicians and Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204, 222 (D.D.C. 2002). The court did not reach this conclusion based on the merits of the rule, but rather found that the FDA lacked statutory authority to promulgate the pediatric rule. Id.

Late last year Congress passed, and the President signed into law, The Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, 117 Stat. 1936 (2003). The new law amends the FDCA by adding section 505B, Research into Pediatric Uses for Drugs and Biological Products. Section 505B basically codifies the pediatric rule. While the new law does not specifically address suitability petitions, the preamble to the pediatric rule did:

> FDA notes that petitions submitted under section 505(j)(2)(C) for a change in active ingredient, dosage form, or route of administration may be denied if "investigations must be conducted to show the safety and effectiveness of" the change. Thus, if a [suitability] petition is submitted

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[3] Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients ("Pediatric Rule"), 21 C.F.R. §§ 201, 312, 314, 601, 63 Fed. Reg. 66,632 (Dec. 2, 1998).

> for a change that would require pediatric study under this rule, the petition may be denied.

63 Fed. Reg. 66,632, 66,641 (Dec. 2, 1998) (quoting the FDCA).

Thus, if FDA accepts petitioner's own characterization of the changes it proposes, the agency should deny the suitability petition and require that the applicant assess the safety and effectiveness of the "new dosage forms" in pediatric patients.

II. The prefilled syringe products will be subject to 180-day exclusivity, if any.

The foregoing discussion notwithstanding, in the event that FDA grants Abbott's request with respect to the two prefilled syringe products, which contain 2 milliliters and 4 milliliters, respectively, of ondansetron hydrochloride in the already approved strength, i.e., 2 mg/ml, it should remind Abbott that such products do not differ from the reference listed drug and will therefore be subject to the 180-day exclusivity, if any, of a generic version of the 2 mg/ml product.

Both of Abbott's proposed prefilled syringe products are the same strength as the reference listed drug. Abbott's proposed change to provide the 2 mg/ml strength in a 2 milliliter prefilled syringe is exactly the same drug as the reference listed drug, i.e., 2 milligrams of ondansetron per milliliter in a 2 milliliter intravenous dosage form. Both products contain 2 milligrams of ondansetron per milliliter and both are single-unit dosage forms. The only difference is the container (i.e., vial vs. syringe). Doubling the volume of the container (8 mg/4 ml syringe) does not create a different product. That is, the reference drug, a product containing 4 milligrams of ondansetron in a 2 milliliter container, and Abbott's proposed product containing 8 milligrams of ondansetron in a 4 milliliter container are the same. The only difference is the size of the container.

FDA apparently has an informal policy of requiring suitability petitions for parenteral drug products where the only change from the reference listed drug is the size of the container, not the strength of the drug. Although we are not challenging the wisdom or legality of such a policy at this time, we likewise do not concede that FDA's policy is consistent with the statute. Nevertheless, it is important to acknowledge that a product like the one at issue here – the 8 mg/4 ml prefilled syringe – is the same as the reference listed drug, particularly with regard to its strength.

The strength of a parenteral drug is the amount of active ingredient in a specified weight or volume of the drug, expressed as a concentration or as a percentage. Thus, the strength of the 4 mg/2 ml vial (listed drug) and the 8 mg/4 ml prefilled syringe is the same: 2 mg/ml. These are not different drugs, they are the same drug in a different size (volume) container. This distinction is important because applicability of certain provisions of FDCA section 505 depend upon whether an ANDA relates to a distinct drug product. And one of the attributes of a distinct drug product is its strength.

The Waxman-Hatch 180-day generic drug exclusivity provision of FDCA section 505 is affected by how FDA defines "strength." That provision provides exclusivity to a "previous application" for "a drug" when that application contains a paragraph IV certification with respect to listed patents. 21 U.S.C. § 355(j)(5)(B)(iv). The FDA's position with regard to different strength products is as follows:

> The agency has determined that each strength of a drug product can be independently eligible for exclusivity. Applicants may be eligible for a separate exclusivity period for each particular strength of the drug product in an ANDA when each strength refers to a different listed drug . . .. The agency, therefore, has determined that each strength of a drug product is itself a listed drug.

180-Day Generic Drug Exclusivity for Abbreviated New Drug Applications; Proposed Rule 64 Fed. Reg. 42873, 42881-82 (Aug. 6, 1999).

We assume that this is a correct interpretation of the statute. As such, it is important to recognize that the same strength drug packaged in a different size container (e.g. Abbott's proposed 8 mg/4 ml prefilled syringe) is not a distinct drug product as compared to the reference listed drug. Although it may be within FDA's discretion to require that a suitability petition be filed for such a product, there should be no impact on 180-day exclusivity. It is our understanding that FDA has adopted and adhered in previous matters to the interpretation we propose. That is, FDA has in the past recognized that the 180-day exclusivity granted to a first filer of a paragraph IV certification for the reference listed drug blocks a subsequent ANDA where a change to a different fill volume (but not a change to the drug's strength) was authorized under section 505(j)(2)(C). This policy is

consistent with the manner in which the products are listed in the Orange Book.[4] Each injectable ondansetron product is listed by concentration, not fill volume.

Conclusion

For all the aforementioned reasons, the undersigned respectfully requests that FDA deny the Abbott suitability petition. In the event that FDA approves the suitability petition in whole or in part, we request that Abbott be advised that the two prefilled syringe products are subject to the 180-day exclusivity, if any, of a first filer of a paragraph IV certification for the reference listed drug.

Sincerely,

Robert A. Dormer
Anne Marie Murphy

RAD/AMM/vam

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4 Approved Drug Products with Therapeutic Equivalence Evaluations ("The Orange Book") (23rd Edition 2003).